UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,371	04/08/2002	Gregor Cevc	2200437-00120US1/VOS-020	1865

23483 7590 12/11/2008

WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER
HISSONG, BRUCE D

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
12/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	09/890,371	CEVC ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/2/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-63 and 65-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-63 and 65-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/02/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 10/02/2008 has been entered.

2. Claims 54-63 and 65-103 are currently pending and are the subject of this office action.

Information Disclosure Statement

The information disclosure statement received on 10/2/2008 has been fully considered.

Specification

Objection to the specification regarding sections of the specification which were not readable, as set forth on page 2 of the office action mailed on 4/3/2008, is *withdrawn* in response to Applicants' submission of a readable copy of page 27.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-63 and 65-103 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for methods of transnasally administering a composition comprised of any two substances other than a surfactant and a lipid, as set forth on pages 2-4 of the office action mailed on 4/3/2008.

The claims are drawn to a method for transnasally administering a pharmaceutical composition to a patient in need thereof, wherein said composition comprises an active ingredient and a carrier

comprising a penetrant suspended or dispersed in a solvent, wherein said penetrant is surrounded by a coating of at least one layer of two substances differing by at least a factor of 10 in solubility in a liquid medium, and wherein the less soluble substance is a lipid and the more soluble substance is a surfactant or a more soluble form of the lipid. In the office action mailed on 10/10/2007, the claims were found to not be enabled because the Applicants had previously asserted that compositions comprising didecanoyl-L-alpha-phosphatidylcholine would not be expected "to form a carrier with a penetrant including layers and aggregates with a diameter as claimed (and is expected to instead self-assemble into small aggregates in micellar form)". Because the specification did not teach what would differentiate a lipid which suitable for use with the claimed penetrant from those that are not suitable, the claims were found to be non-enabled.

In the response received on 10/2/2008, the Applicants argue that the specification and claims provide ample information on how to prepare suitable penetrant compositions with lipids and surfactants as claimed. The Applicants assert that the claims explicitly recite required functional properties of the claimed penetrant composition, and the specification lists various lipids and surfactants suitable for use in the claimed penetrant, and provides guidance as to the selection of suitable materials. Furthermore, the declaration by Dr. Cevc explains the role of the shape and form of the claimed penetrant formed by two substances which differ in solubility by at least a factor of 10. In particular, the claims require the less soluble of the two substances to be a lipid and the more soluble substance to be a surfactant or a less soluble form of the lipid. The Cevc declaration asserts that the "Drejer phosphatidylcholine" (didecanoyl-L-alpha-phosphatidylcholine) cannot form large bilayer vesicle aggregates, but would instead self-assemble into small aggregates in micellar form because this particular phosphatidylcholine exhibits high solubility due to it's shorter acyl chain length. For this reason, one of ordinary skill in the art would recognize that the more soluble "Drejer phosphatidylcholine" would not be suitable for use in creating penetrant compositions which the recited features of the instant claims. Therefore, because the specification specifically teaches that the less soluble self-aggregating molecule is a lipid and the more soluble component is a surfactant, and a person of skill in the art would be knowledgeable regarding the solubility of various lipid and surfactant compounds, the specification is enabling for the currently claimed invention.

These arguments have been fully considered and are persuasive with regards to the selection of lipids and surfactants which appropriately differ in terms of solubility. However, upon further consideration, the claims have been determined to be enabled for a method of transnasally administering a compound comprising a peptide/protein active ingredient and further comprising a penetrant comprised of

soybean phosphatidylcholine and either Tween 80 or sodium cholate, but are not enabled for a method of transnasally administering a composition comprising any other active ingredient and/or a penetrant comprised of any other substances. As currently written, the breadth of the claims is excessive in that the claims read on a method of transnasally administering a compound comprising an active ingredient and a penetrant composition comprising any lipid and surfactant or less soluble form of the lipid, as long as the lipid and the surfactant differ by a factor of 10 in terms of solubility and the lipid is the less soluble component. The specification provides guidance and examples showing that compositions comprising soybean phosphatidylcholine as the lipid, and either sodium cholate or Tween 80 as the surfactant are capable of use for transnasal administration. However, it is known in the art that nasal administration is not always effective. Santus *et al* (US 6,333,044) teaches that while some compounds may be effectively administered nasally, it cannot be presumed that all therapeutic agents can be administered by this route. Santus *et al* specifically teaches that nasal administration of therapeutic agents has been limited to some peptide/protein molecules, such as calcitonin, cerulean, β-endorphin, glucagon, horseradish peroxidase, β-interferon, oxytocin, and insulin). Furthermore, Santus *et al* states that the "ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous membranes. In fact, mucous membrane irritation caused by the drug and/or excipient is the most common reason for which intranasal administration has not gained wider acceptance." (column 2, lines 40-59). Therefore, in light of the disclosure of Santus et al, a person of ordinary skill in the art would know that nasal administration of all types of active ingredients is unpredictable, and would also know that mucous membrane irritation is a major obstacle in nasal administration. The specification has exemplified nasal administration of peptide/protein active ingredients (e.g. insulin) using a penetrant comprising soybean phosphatidylcholine and either sodium cholate or Tween 80. However, the specification has not shown effective nasal administration of any other type of active ingredient, or well-tolerated administration using any other lipid/surfactant combination. Thus, a person of ordinary skill in the art would not be able to predict which other active ingredients, or which other lipid/surfactant combinations, could be effectively administered via the nasal route and also not cause unacceptable nasal mucous membrane irritation. Such predictions would require further, undue experimentation, and therefore while the specification is enabling for methods of nasally administering peptide/protein active agents with a soybean phosphatidylcholine/Tween 80/sodium cholate penetrant, the specification is not enabling for the full breath of the claims.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 54-63 and 65-103 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for methods of transnasally administering a composition comprised of any two substances other than a surfactant and a lipid, as set forth on pages 2-4 of the office action mailed on 4/3/2008.

In the response received on 10/2/2008, the Applicants argue that the specification provides sufficient description of a representative number of lipids and surfactants that can be used, and the independent claims 54 and 100 set forth a detailed description of the functional characteristics that must be possessed by the lipid and surfactant substances in order to form a suitable penetrant. Additionally, the specification lists numerous lipids and surfactants suitable for use in the claimed penetrants. The specification and the claims also require at least two substances which differ by a factor of 10 in terms of solubility, and require that the less soluble substance be a lipid, and the more soluble substance be a surfactant or a more soluble form of the lipid. The Applicants argue that this requirement for the less soluble substance to be a lipid and the more soluble substance to be a surfactant or more soluble form of the lipid provides a person of skill in the art with sufficient description to both (a) produce the functional characteristics of the composition recited in claims 54 and 100, and (b) differentiate functional lipids from those that would not be functional in the claimed penetrant composition. The Applicants further assert that the Cevc declaration describes the types of observations one skilled in the art would readily make to appreciate which materials do or do not exhibit the claimed functional characteristics. Therefore, the specification and the claims, in view of the knowledge of one having ordinary skill in the art, provide sufficient description to support the claimed invention.

These arguments have been fully considered and are persuasive in view of the fact that the level of knowledge and skill of a person skilled in the art is high, and a person of skill in the art could differentiate various lipids and surfactants based on relative solubility, and thus no rejection will be made regarding the genus of lipid and surfactant compounds which are suitable to form a penetrant compound with the recited physical/chemical limitations.

However, upon further consideration, it is noted that nasal administration of substances is notoriously unpredictable with regards to the ability of various compounds to be administered via this route, and with regards to undesirable side-effects, as discussed above. The Applicants have described nasal administration of insulin using a penetrant compound comprised of soybean phosphatidylcholine and either sodium cholate or Tween 80. However, although the specification describes many suitable lipids and surfactants in terms of structure and function with respect to their ability to form a penetrant composition with the cited physical/chemical limitations, this structure/function description is not

adequate to describe which compounds could be used in the claimed methods of nasal administration. A person of skill in the art would know that many compounds used in transnasal administration provoke inflammation of the nasal mucosa, and the instant specification does not describe which compounds, other than soybean phosphatidycholine and either sodium cholate or Tween 80, can be safely administered in a method of transnasal administration. Therefore, the genus of penetrant compounds which can effectively and safely delivery an active ingredient via transnasal administration has not been adequately described.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647